Objective: To evaluate the intraoperative use of mitomycin to improve the surgical outcome and reduce the rate of soft tissue restenosis in children undergoing choanal atresia repair.

Design: Retrospective chart review of all patients surgically treated for congenital choanal atresia by the senior author (W.F.M).

Setting: Tertiary children’s hospital.

Patients: Eight consecutive patients with bony choanal atresia (6 unilateral and 2 bilateral) were compared with 15 historical controls (6 unilateral and 9 bilateral). All study and historical control patients were treated with soft plastic postoperative stenting.

Intervention: At the completion of the surgical repair of the choanal atresia, 0.4 mg/mL of topical mitomycin was applied to the posterior choanae for 3 minutes.

Main Outcome Measure: The success rate of the repair of the choanal atresia as determined by the postoperative need for dilation or revision surgical procedures was compared with that of the historical controls.

Results: All 8 children with intraoperative use of mitomycin were treated with a mean ± SEM of 0.375±0.183 dilations per patient. The 15 children in the control group received a mean ± SEM of 3.667±0.583 postoperative dilations for soft tissue restenosis. The difference in the number of postoperative dilations between the study and control group was statistically significant (P = .006) using a t test.

Conclusions: Mitomycin is an effective and reliable treatment for improving the surgical outcome for choanal atresia repair. This may obviate the need for postoperative dilations and may potentially eliminate the need for surgical stenting.


Surgical Management of Choanal Atresia

Improved Outcome Using Mitomycin

Bradford W. Holland, MD; William F. McGuirt, Jr, MD

The surgical treatment of congenital choanal atresia is one of the more challenging endeavors within the realm of pediatric otolaryngology. The symptoms of choanal atresia largely depend on whether the condition is unilateral or bilateral; those with bilateral disease present early with life-threatening respiratory difficulty, whereas those with unilateral atresia may present in childhood or young adulthood with unilateral nasal obstruction and rhinorrhea. The atresia itself may be classified as bony, mixed bony and membranous, or purely membranous, although the latter may be rare.¹ There are numerous methods for correcting this condition, but the current most commonly used methods are the transpalatal approach,²,³ the transeptal approach,⁴,⁵ and the endoscopic transnasal approach.⁶,⁷ Factors that influence the type of approach selected and its subsequent success include the age of the patient, the size of the nasopharynx, the thickness of the atresia, bilateral vs unilateral atresia, the use of postoperative stenting, the surgeon’s preference of approach, and the presence of other anomalies such as found in the CHARGE association (a malformation syndrome that includes coloboma, hearing deficit, choanal atresia, retardation of growth, genital defects, and endocardial cushion defect).

Once the atresia is surgically corrected, the surgeon is often faced with the problem of restenosis. Pirsig³ noted in 1986 that

Re-stenosis mainly becomes a problem because of the small dimensions of the atretic area, and usually starts from the lateral and cranial borders of the new nasal opening or develops from excessive granulation tissue.

The rates of restenosis vary widely and range from 0% to 85%, although many authors writing on the subject of surgical success do not comment on the need for postopera-
PATIENTS AND METHODS

PATIENTS

We reviewed all charts of patients who had undergone surgical correction of choanal atresia within the past 8 years. Only those cases in which the surgical procedure was performed by the senior author (W.F.M.) were selected. Records were analyzed for demographic information including age at repair, race, sex, and presence of other syndromic features. Data were collected on the type and location of atresia, type of repair, length of stenting, need for subsequent dilations, and follow-up. The charts were examined to determine if mitomycin had been applied topically (study group) or not (control group).

SURGICAL METHODS

Informed consent was obtained prior to the surgical procedure. The transpalatal repair was performed as outlined by Owens.2 Endoscopic transnasal repair was performed according to previously described methods.19 After the atretic area was opened and the mucosal flaps seated, mitomycin (Mutamycin; Bristol Laboratories, Princeton, NJ) in a concentration of 0.4 mg/mL was used to soak a neurocottonoid pledget, which was then held against the mucosa for 3 minutes on each side. Postoperative stenting was performed with 2.5- to 4.5-mm (inner diameter) endotracheal tubing (ETT); the size was selected to achieve an adequate airway and snug fit within each patient’s nose. For the neonates, a 2.5– or 3-mm ETT was used to make a stent; for children, a 4.5-mm ETT was typically used. Patients were discharged with nasal saline drops and instructions to apply the drops to keep the stents patent. Postoperative antibiotics were not used in this study.

The stents were left in for the periods indicated in Table 1 and Table 2. On stent removal, any granulation tissue or restenosis of the area treated was noted. If any obstructing granulation tissue was found, it was removed, and if restenosis was present, nasal dilations were performed with urethral sounds to the appropriate diameter. Most commonly, additional dilations were performed only if the patient became symptomatic or if the posterior choana was stenotic on physical examination. Antibiotics, oxymetazoline nasal spray, and dexamethasone nasal drops (0.1%, 2 to 3 drops in each nostril twice daily) were used only if the patient developed inflammation associated with upper respiratory tract infection after the stents had been removed. All control group patients have been observed for at least 1 year, and in many cases, as many as 8 years. The study group has had more limited follow-up, with a range of 1 to 18 months and a median follow-up of 8.5 months.

Table 1. Patients Treated With Mitomycin*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Type of Atresia</th>
<th>Type of Repair</th>
<th>Age at Repair</th>
<th>Duration of Stenting, wk</th>
<th>No. of Dilations</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BB</td>
<td>Transpalatal</td>
<td>14 d</td>
<td>5</td>
<td>1 (8 wk after stent removal)</td>
<td>CHARGE</td>
</tr>
<tr>
<td>2</td>
<td>BB</td>
<td>Transpalatal</td>
<td>6 wk</td>
<td>6</td>
<td>0</td>
<td>CHARGE</td>
</tr>
<tr>
<td>3</td>
<td>UB</td>
<td>Transpalatal</td>
<td>5 mo</td>
<td>4</td>
<td>0</td>
<td>Healthy</td>
</tr>
<tr>
<td>4</td>
<td>UBM</td>
<td>Transpalatal</td>
<td>14 mo</td>
<td>6</td>
<td>0</td>
<td>Healthy</td>
</tr>
<tr>
<td>5</td>
<td>UB</td>
<td>Transpalatal</td>
<td>15 mo</td>
<td>2</td>
<td>1 (on stent removal)</td>
<td>CHARGE</td>
</tr>
<tr>
<td>6</td>
<td>UM</td>
<td>Endoscopic transnasal</td>
<td>6 y</td>
<td>6</td>
<td>0</td>
<td>Healthy</td>
</tr>
<tr>
<td>7</td>
<td>UM</td>
<td>Endoscopic transnasal</td>
<td>10 y</td>
<td>6</td>
<td>0</td>
<td>Healthy</td>
</tr>
<tr>
<td>8</td>
<td>UB</td>
<td>Transpalatal</td>
<td>12 y</td>
<td>8</td>
<td>1 (on stent removal)</td>
<td>Healthy</td>
</tr>
</tbody>
</table>

*BB indicates bilateral, bony; UB, unilateral, bony; UBM, unilateral, mixed bony and membranous; UM, unilateral membranous; and CHARGE, syndrome that includes coloboma, hearing deficit, choanal atresia, retardation of growth, genital defects, and endocardial cushion defect.

We report the use of topical mitomycin in 8 patients to improve the success of surgical therapy for congenital choanal atresia. We further speculate on future investigations and possible roles for mitomycin as a topical agent in airway mucosal surgery.

RESULTS

Eight patients with congenital choanal atresia had mitomycin applied intraoperatively during their surgical repair.
Five were male, and 3 were female. Six were white, and 2 were African American. The age of these patients ranged from 14 days to 12 years, with an average age of 3.8 years. Two patients had bilateral choanal atresia, and 6 had unilateral atresia. The atresia was composed of a bony plate in 5 and a mixed membranous and bony plate in the remaining 3. Three patients had CHARGE association, and the remaining 5 were otherwise healthy. Six had transpalatal repairs, and 2 had endoscopic transnasal repairs. The period of stenting ranged from 2 to 8 weeks, with average of 5.4 weeks. Postoperative dilations were required only 1 time in 3 of the 8 patients, and no patient required more than 1 dilation. On stent removal, no granulation tissue or granuloma formation was noted in any patient (Figures 1, 2, 3, and 4).

There were 15 patients in the control group who did not receive mitomycin (Table 2). Seven (47%) were male, and 8 (53%) were female. Ten (67%) of the 15 patients were white, 3 (20%) were African American, 1 (7%) was Hispanic, and 1 (7%) was Asian. The age of these patients ranged from 7 days to 11 years. The average age was 2.7 years. Nine patients (60%) had bilateral choanal atresia, and 6 (40%) had unilateral atresia. The atresia was composed of a bony plate in 8 patients (53%) and a mixed membranous and bony plate in the remaining 7 (47%). Nine patients (60%) had CHARGE association or other syndromic features, and the remaining 6 (40%) were otherwise healthy. Twelve patients (80%) had transpalatal repairs, and 3 (20%) had endoscopic transnasal repairs. The period of stenting ranged from 3 to 8 weeks, with an average of 5.6 weeks. Only 1 patient (7%) did...

Table 2. Patients Not Treated With Mitomycin*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Type of Atresia</th>
<th>Type of Repair</th>
<th>Age at Repair</th>
<th>Duration of Stenting, wk</th>
<th>No. of Dilations</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BB</td>
<td>Transpalatal</td>
<td>7 d</td>
<td>6</td>
<td>4</td>
<td>Autosomal dominant PDA, bladder and hand deformities</td>
</tr>
<tr>
<td>2</td>
<td>BB</td>
<td>Transpalatal</td>
<td>2 wk</td>
<td>6</td>
<td>3</td>
<td>9p syndrome</td>
</tr>
<tr>
<td>3</td>
<td>BBM</td>
<td>Transpalatal</td>
<td>8 wk</td>
<td>6</td>
<td>6</td>
<td>VSD, PDA, CHARGE (incomplete)</td>
</tr>
<tr>
<td>4</td>
<td>BB</td>
<td>Transpalatal</td>
<td>5 mo</td>
<td>6</td>
<td>6</td>
<td>CHARGE</td>
</tr>
<tr>
<td>5</td>
<td>BBM</td>
<td>Transpalatal</td>
<td>10 mo</td>
<td>6</td>
<td>4</td>
<td>Goldenhar syndrome</td>
</tr>
<tr>
<td>6</td>
<td>BB</td>
<td>Transpalatal</td>
<td>1.5 y</td>
<td>6</td>
<td>3</td>
<td>CHARGE</td>
</tr>
<tr>
<td>7</td>
<td>UB</td>
<td>Transpalatal</td>
<td>1.5 y</td>
<td>10</td>
<td>10</td>
<td>Healthy</td>
</tr>
<tr>
<td>8</td>
<td>BB</td>
<td>Transpalatal</td>
<td>1.5 y</td>
<td>5</td>
<td>2</td>
<td>Healthy</td>
</tr>
<tr>
<td>9</td>
<td>UBM</td>
<td>Endoscopic transnasal</td>
<td>2.5 y</td>
<td>5</td>
<td>2</td>
<td>CHARGE, prior tracheotomy</td>
</tr>
<tr>
<td>10</td>
<td>BB</td>
<td>Transpalatal</td>
<td>3.5 y</td>
<td>5</td>
<td>4</td>
<td>Healthy</td>
</tr>
<tr>
<td>11</td>
<td>UB</td>
<td>Transpalatal</td>
<td>4 y</td>
<td>6</td>
<td>3</td>
<td>Healthy</td>
</tr>
<tr>
<td>12</td>
<td>BB</td>
<td>Transpalatal</td>
<td>4 y</td>
<td>8</td>
<td>3</td>
<td>CHARGE, prior tracheotomy</td>
</tr>
<tr>
<td>13</td>
<td>UBM</td>
<td>Endoscopic transnasal</td>
<td>5 y</td>
<td>6</td>
<td>4</td>
<td>Healthy</td>
</tr>
<tr>
<td>14</td>
<td>UBM</td>
<td>Endoscopic transnasal</td>
<td>5 y</td>
<td>6</td>
<td>3</td>
<td>Healthy</td>
</tr>
<tr>
<td>15</td>
<td>UB</td>
<td>Endoscopic transnasal</td>
<td>11 y</td>
<td>6</td>
<td>1</td>
<td>Healthy</td>
</tr>
</tbody>
</table>

*BB indicates bilateral, bony; BBM, bilateral, mixed bony and membranous; UB, unilateral, bony; UBM, unilateral, mixed bony and membranous; PDA, patent ductus arteriosus; VSD, ventriculoseptal defect; and CHARGE, syndrome that includes coloboma, hearing deficit, choanal atresia, retardation of growth, genital defects, and endocardial cushion defect.
†Required reinsertion of stents twice after initial stents were removed.
not require postoperative dilations. The rest (14 [93%]) required at least 1 dilation, with a range of 1 to 10 dilations per patient. Granulation tissue was noted on stent removal in 11 (73%) of the 15 patients.

The study group was compared with the control group. No statistical difference was found when compared on the basis of age, type of atresia, presence of other syndromic findings, type of repair, or length of stenting. When compared on the basis of postoperative dilations, the study group required a mean ± SEM of 0.375±0.183 postoperative dilations, whereas the control group required a mean ± SEM of 3.667±0.583 dilations. This difference was statistically significant ($P=0.006$) using a $t$ test. Statistical analysis also showed that the control group was 3 times more likely to develop granulation tissue than the study group (95% confidence interval, 1.3-6.7; $P=0.006$). The difference in the rate of synechia formation between the study and control groups was not statistically significant, although the low rate of synechia formation in both groups and the relatively small sample size preclude definitive assumptions about this association.

**COMMENT**

Success in repairing congenital choanal atresia depends on numerous factors. Among them are the age of the patient, the type of atresia (bony vs membranous; unilateral vs bilateral), the presence of other congenital anomalies, the type of stent used and the time it is left in place, and most controversially, the approach used to perform the repair. Even the definition of success is variable; some authors believe that any need for dilation in the postoperative period for up to 1 year represents surgical failure, whereas others report surgical successes for those patients who may have had dilations but did not require revision surgery. Not all authors report whether or not their patients required postoperative dilations to maintain nasal patency. The extreme variability in the number of dilations, length of stenting, and postoperative care make comparison between different authors difficult. Whatever the definition of success, failure due to granulation tissue and restenosis represents one of the main obstacles to surgical success. Any therapy that reduces the granulation tissue formation and reduces or eliminates restenosis and the need for postoperative stenting would be of great value. In our experience these complications have developed regardless of surgical approach and technique. Therefore, it would seem appropriate to search for medical therapies that might improve the surgical outcome in choanal atresia repair.

Medical treatments have improved the outcome of congenital choanal atresia repair. Antibiotics are used by many authors prophylactically as long as the stents are left in place or for unspecified periods. Others use antibiotics only if infection and granulation tissue are found as a result of stenting. Beste et al have described 4 patients who experienced gastroesophageal reflux (GER), which was thought to cause granulation tissue formation and restenosis. They advocated controlling for GER within the postoperative period and leaving intranasal stents in place 3 to 4 weeks after the GER was controlled. Although this was a prospective study, there was no randomization of patients who received medical therapy for GER. We have found no prospective randomized controlled studies investigating the use of medical adjuncts for surgical therapy.

Topical therapy has been used in a limited and anecdotal fashion in treating choanal atresia. Intranasal steroids have been used by some authors, although no information was given about the concentration or frequency of use, and few comments were made about their efficacy other than that they may reduce stenosis and granulation tissue formation. Krespi et al used topical peroxide drops on all their patients undergoing transseptal repairs, but did not comment on the benefit of this therapy over the use of saline. Indeed, the only topical therapy that is nearly universal is nasal saline drops and fre-
quent suctioning to maintain stent patency. This intuitively makes sense because the diameter of the stents used are usually small, and crusting leading to obstruction is seen in nearly every case when saline drops are not used. But to our knowledge, any scientific evidence that would demonstrate the benefit of topical therapy after surgery for choanal atresia is nonexistent.

Mitomycin is an antitumor alkylating agent shown to have an inhibitory effect on fibroblast proliferation. Although most commonly used in an intravenous form as a chemotherapeutic agent, it has been used topically to prevent stenosis and improve outcome in ophthalmic glaucoma-filtering surgery. Findings from cultured fibroblasts have shown that exposure to 0.4 mg/mL of mitomycin for 1 minute and 5 minutes caused a 77% and 90% reduction in \( ^{3}H \)-thymidine uptake, respectively.\(^{17} \) At this concentration, the drug is not cytotoxic to fibroblasts, but concentrations of 1 mg/mL (1%) and higher are cytotoxic. Because it is an alkylating agent, mitomycin inhibits fibroblast proliferation by cross-linking DNA and therefore affects all cells, not only those that are actively synthesizing DNA. Mitomycin has recently been investigated in rabbit models in which it was used topically after maxillary antrotomy\(^{17} \); it reduced the rate of restenosis of the antrotomies, and the surrounding nasal ciliary epithelium regained its normal microscopic morphologic characteristics and physiologic mucociliary clearance within 2 weeks of application. Thus, it seems that mitomycin should be ideal in reducing fibroblast proliferation and restenosis without causing any long-term harm to the surrounding mucosa.

We have used mitomycin on 8 patients undergoing repair for choanal atresia. All patients had soft stents placed postoperatively. Although there were no outright failures in either the study group or the control group, we observed a certain rate of restenosis and formation of granulation tissue in patients who were not treated with mitomycin. It generally seemed that granulation tissue found at the time of stent removal was an ominous sign, and the more granulation present, the more likely the patient was to restenose. The patients in the control group who had granulation tissue at stent removal were the same patients who required numerous dilations. Conversely, those who did not have granulation tissue at the time of stent removal usually required the fewest dilations, and in 1 case (Table 2, patient 7), no dilations. The patients treated with mitomycin did not develop granulation tissue or granulomas, and this was the most notable difference between the study and control groups. In fact, the control group was 3 times as likely to develop granulation tissue than the study group (\( P<.01 \)). The study group did not develop restenosis at the same rate as the control group, although postoperative dilations were not completely avoided in either group.

Follow-up has been limited in the study group (median, 8.5 months), and is less than the control group, who have all been observed for at least 1 year. We realize that this is a limitation of this study, but we also note that all patients in the control group who developed restenosis did so within 1 to 2 months of stent removal. We have observed all patients in the study group for at least 5 months, with the exception of 1. Because nearly all of the patients have passed this critical period for the development of restenosis, we believe that these statistical analyses showing the benefits of mitomycin are valid and the advantageous effect of this drug is real.

If an effort to identify any bias existing between the 2 groups, the study group and control group were statistically analyzed and compared. No statistically significant differences were found when the 2 groups were compared on the basis of the duration of stenting, age at repair, type of atresia, type of repair, or presence of other syndromic findings. There was a tendency for the control group to have a higher percentage of bilateral atresia (60%) when compared with the study group (25%). This difference was not statistically significant, but given the small numbers in this series, the difference might have adversely affected the outcome of the control group. Patients in this study were not evaluated or treated for reflux, which potentially represents an uncontrolled variable in our population. Despite these limitations, the 2 groups seem statistically similar enough to validate the beneficial effects of mitomycin.

Mitomycin has only recently been introduced into the field of otorhinolaryngology, and most of the investigations of its use have involved the treatment of subglottic stenosis in both animals and humans. In airway stenosis, granulation tissue leads to cicatrix formation and stenosis.\(^{18} \) In treating subglottic stenosis, antibiotics, steroids (local or systemic), anti-reflux medication, and meticulous local hygiene reduce the formation of granulation tissue and thus the rate of restenosis.\(^{13} \) We believe the same principles apply to the treatment of choanal atresia, and that other analogies between the 2 disease processes are possible. Canine studies have shown that much higher concentrations of mitomycin (10 mg/mL, or 25 times the dose used in this series) produce excellent results when applied topically. The actual dose received by our patients with topical cotton pledget application was likely more dilute than the original concentration of 0.4 mg/mL placed on the pledget due to surrounding blood and mucous as well as other fluids being absorbed by the pledget for the 3 minutes it was held in the choanae. Using higher concentrations may help overcome this dilution and prove more effective. Higher doses have the potential to cause systemic adverse effects (which can include bone marrow suppression and hemolytic-uremic syndrome), but no systemic adverse effects have been reported with topical mitomycin therapy. Results from other canine subglottic studies have shown that a second application 2 days after the initial application did not improve overall outcome.\(^{13} \) Thus, one would not expect additional treatments with mitomycin to show any advantage over a single treatment, although this is purely speculative.

We believe that medical therapy can improve the outcome of choanal atresia surgery and, specifically, that topical therapy may have a unique role. With recent advances in the field of growth factor modification and wound healing, the realm of possible topical or systemic medical treatments remains wide open. Additionally, other antineoplastic agents, such as fluorouracil, have antifibroblastic activity and may themselves have future...
Topical mitomycin seems to have antifibroblastic activity that improves the outcome of surgical treatment of choanal atresia by eliminating postoperative granulation tissue and reducing the rate of restenosis. This preliminary study has shown initial success, but further prospective randomized studies are needed to fully understand the benefits of this therapy and to answer questions regarding dose, length of treatment, and use of other topical adjuvant therapy.

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